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(54) Title: AN IMPROVED FORM OF FORM I CELIPROLOL HYDROCHLORIDE

(57) Abstract: A novel process for the production of an improved form of Form I celiprolol hydrochloride, N'-[3-Acetyl-4-[(1,1-dimethylethyl)amino]-2-hydroxy-propoxy]phenyl]-N,N-diethyl urea hydrochloride, is described.

AN IMPROVED FORM OF

FORM I CELIPROLOL HYDROCHLORIDE

FIELD OF THE INVENTION

The present invention relates to an improved form of Form I celiprolol hydrochloride and a process for the production thereof.

BACKGROUND OF THE INVENTION

Chemically celiprolol is N'-[3-Acetyl-4-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenyl]-N,N-diethyl urea and belongs to the β-blocker class of antihypertensive agents. A literature search revealed that celiprolol hydrochloride exists in several polymorphic modifications and that these can be distinguished by their infrared spectral characteristics and x-ray diffraction patterns (Burger et al Acta. Pharm. Technol., 34(3), 147-151 (1988); Sugiyama et al., Iyakuhin Kenkyu, 21(1), 27-39, (1990). However, there exist conflicting reports in the literature regarding identification of Form I celiprolol hydrochloride. For example, the infrared spectral data of Form I celiprolol hydrochloride given in Acta. Pharm. Technol., 34(3), 147-151(1988), differs from the one given in Drug Development and Industrial Pharmacy, 14 (4), 465-474 (1988). They also differ in their melting points. While there are a few instances where celiprolol hydrochloride has been synthesized, none of them mention which polymorph has been obtained. The only example of a method for preparation of Form I celiprolol hydrochloride that we came across was

one where Form 1 celiprolol hydrochloride is prepared by recrystallization from methanol-diethyl ether. However, this method did not give us Form I celiprolol hydrochloride. It has been mentioned in 'Analytical Profiles of Drug Substances', Vol. 20 that Form I celiprolol hydrochloride can be obtained from organic solvents under a wide variety of conditions but no method has been described which results in Form I celiprolol hydrochloride.

Celiprolol hydrochloride has been prepared by treating celiprolol base in acetone with aqueous hydrochloric acid [Arzneim. Forsch., 33(1), 2-4 (1983)]. However, this method generally gave mixtures of Form I and Form II celiprolol hydrochloride, or Form II celiprolol hydrochloride exclusively. Further, this method suffers from difficulties in work-up such as difficulties in stirring and slow filtration.

SUMMARY OF THE INVENTION

An object of this invention is to produce an improved form of Form I celiprolol hydrochloride which has highly desirable handling properties such as filtration, drying characteristics and flowability.

It is a further object of this invention to provide a process which produces an improved form of Form I celiprolol hydrochloride consistently and with good yields.

According to one aspect of the invention, a new process for producing Form I celiprolol hydrochloride having improved filtration and drying characteristics is provided. The process comprises dissolving celiprolol base or Form II

celiprolol hydrochloride in a water-miscible organic solvent or a homogeneous mixture of the aforesaid solvents and water, adding hydrochloric acid and subsequently recovering improved form of Form I celiprolol hydrochloride from the solution thereof. The water-miscible organic solvent or solvents has the characteristic that it solubilizes celiprolol base and hydrochloric acid and precipitates the desired form of Form I celiprolol hydrochloride, slowly and uniformly.

Generally, the process is carried out at a temperature ranging from about ambient to the reflux temperature of the solvent used. More preferably, it is carried out at ambient temperature.

Suitable water-miscible organic solvents include the group consisting of ketones, e.g., acetone; alcohols, e.g., ethanol, isopropyl alcohol, n-propanol or n-butanol; acetonitrile; tetrahydrofuran; dioxan; and mixtures thereof.

Methods known in the art can be used with the process of this invention to enhance any aspect of this process. For example, the solution containing celiprolol base may be seeded with crystals of Form I celiprolol hydrochloride prior to the addition of hydrochloric acid or the slurry may be cooled prior to filtration.

Generally, the product can be recovered by any standard method known in the art such as by filtration, filtration under vacuum, centrifugation or decantation and drying.

According to another aspect of the invention, a new process for consistently producing an improved form of Form I celiprolol hydrochloride is provided.

It has been found that use of celiprolol base having melting point 110-117ºC for the preparation of celiprolol hydrochloride does not give Form I consistently. Surprisingly, we have found that the use of celiprolol base which has been dried at a temperature below 70ºC, more preferably below 55ºC with a moisture content of less than 5% w/w and having melting point 80-100ºC, leads to consistency in achieving Form I celiprolol hydrochloride. Such a base is characterized by its distinct infared spectrum, melting point and x-ray powder diffraction pattern differing from the celiprolol base melting above 110ºC. Depending on the drying time and technique for drying, the moisture content in the celiprolol base may vary from 2-5% w/w but it generally remains as a monohydrate (4.5% w/w water content).

The present invention also provides a process for the conversion of celiprolol hyrochloride Form II to Form I celiprolol hydrochloride using similar conditions for crystallization as those described above which give Form I celiprolol hydrochloride.

Form I celiprolol hydrochloride prepared by the process of the present invention is characterized by its infrared spectral data which matches with the infrared spectrum given in the Analytical profiles of Drug substances.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is illustrated by, but not limited to, the following examples:

EXAMPLE 1

PREPARATION OF FORM I CELIPROLOL HYDROCHLORIDE USING CELIPROLOL FREE BASE

Celiprolol free base (25gm, moisture content 4.71% w/w) was dissolved in a mixture of acetone (395ml) and water (8ml) at 25-30ºC. Activated carbon (2.5gm) was added to the clear solution and stirred for 15 minutes. Filtered it through hyflo bed, cooled the filtrate to about 20ºC and seeded the clear filtrate with celiprolol hydrochloride Form 1 crystals. Added conc. Hydrochloric acid (5.4 ml) slowly till crystallization was complete. The precipitated celiprolol hydrochloride was filtered off, washed with acetone and dried under reduced pressure to give 22.15gm of celiprolol hydrochloride Form 1. IR (KBr) spectrum confirmed that the material was Form I celiprolol hydrochloride.

EXAMPLE 2

Celiprolol free base (12.5gm, moisture content 4.71% w/w) was dissolved in aqueous isopropanol (198ml) at 25-30ºC. Actiivated carbon (1.25gm) was added to the clear solution and stirred for about 30 minutes.

Filtered off the carbon through hyflo bed, cooled the filtrate to about 20ºC and seeded the clear solution with Form I celiprolol hydrochloride crystals. Added conc. Hydrochloric acid (2.7ml) slowly till crystallization was complete. The precipitated celiprolol hydrochloride was filtered off, washed with aqueous isopropanol and dried under vacuum to afford 12.5gm of dry Form I celiprolol hydrochloride. IR (KBr) spectrum confirmed that the material was Form I celiprolol hydrochloride.

EXAMPLE 3

Celiprolol free base (12.5 gm, moisture content 4.71% w/w) was dissolved in aqueous tetrahydrofuran (205ml) at 25-30ºC. Added activated carbon and stirred for 30 minutes. Carbon was removed by filtration through hyflo-bed, seeded the clear filtrate with Form I celiprolol hydrochloride crystals. Added conc. Hydrochloric acid (2.7ml) slowly till crystallization was complete. The precipitated celiprolol hydrochloride was filtered off, washed with aqueous tetrahydrofuran and dried under reduced pressure to give 10.8gm of Form I celiprolol hydrochloride, IR (KBr) spectrum confirmed that material was Form I celiprolol hydrochloride.

EXAMPLE 4

PREPARATION OF FORM I CELIPROLOL HYDROCHLORIDE USING CELIPROLOL FREE BASE.

Celiprolol free base (12.5gm, moisture content 4.71% w/w) was dissolved in acetone (196ml) at 25-30ºC. Activated carbon (1.25gm) was

added to the clear solution and stirred for 15 minutes. Filtered off the carbon through hyflo-bed, cooled the filtrate to about 20ºC and seaded the clear solution with Form I celiprolol hydrochloride crystals. Added conc. Hydrochloric acid slowly till the pH was about 6. The resulting suspension was stirred for about 10 minutes at about 20ºC, filtered the solid, washed with acetone and dried under vacuum to give 12.4 gm of dry Form I celiprolol hydrochloride. IR (KBr) spectrum confirmed that the material was Form I celiprolol hydrochloride.

EXAMPLE 5

PREPARATION OF FORM I CELIPROLOL HYDROCHLORIDE USING FORM I CELIPROLOL HYDROCHLORIDE.

Form I celiprolol hydrochloride (10gm) was suspended in absolute ethanol (50ml) at 55-60ºC overnight and the resulting suspension was refluxed to get a clear solution. Seeded the clear solution with Form I celiprolol hydrochloride crystals. Cooled it to about 10ºC and stirred at this temperature for about 30 minutes. The separated solid was filtered and dried under vacuum to afford 9.5gm of Form I celiprolol hydrochloride. IR (KBr) spectrum confirmed that the material was Form I celiprolol hydrochloride.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

CLAIMS

1. An improved form of Form I celiprolol hydrochloride having improved filtration and drying characteristics, produced by a process comprising dissolving celiprolol base or Form II celiprolol hydrochloride in a water-miscible organic solvent or a homogeneous mixture of the aforesaid solvents and water, adding hydrochloric acid and subsequently recovering improved form of Form I celiprolol hydrochloride from the solution thereof.

2. The process of claim 1 wherein seeds of Form I celiprolol hydrochloride are added to crystallize the improved form of Form I celiprolol hydrochloride.

3. The process of claim 1 wherein said water-miscible organic solvent is selected from the group consisting of ketones, alcohols, acetonitriles, tetrahydrofuran dioxan and mixtures thereof.

4. The process of claim 3 wherein said water-miscible organic solvent is selected from the group consisting of acetone, ethanol, isopropyl alcohol, n-propanol, n-butanol and mixtures thereof.

5. The process of claim 1, 3 and 4 wherein said solvent is acetone or a homogeneous mixture of acetone and water.

6. The process of claim 1 wherein said improved form of Form I celiprolol hydrochloride is recovered by filtration or centrifuging.

7. The process of claim 1 wherein celiprolol base has a moisture content of less than 5% w/w.

8. The process of claim 6 wherein celiprolol base has a moisture content between 2-5% w/w.

9. The process of claim 1 wherein celiprolol base is obtained by drying at a temperature less than 70ºC.

10. The process of claim 9 wherein celiprolol base is obtained by drying at a temperature less than 55ºC.

11. A process for the production of an improved form of Form I celiprolol hydrochloride having improved filtration and drying characteristics, said process comprising dissolving celiprolol base or Form II celiprolol hydrochloride in a water-miscible organic solvent or a homogeneous mixture of the aforesaid solvents and water, adding hydrochloric acid and subsequently recovering improved form of Form I celiprolol hydrochloride from the solution thereof.

12. The process of claim 11 wherein seeds of Form I celiprolol hydrochloride are added to crystallize the improved form of Form I celiprolol hydrochloride.

13. The process of claim 11 wherein said water-miscible organic solvent is selected from the group consisting of ketones, alcohols, acetonitriles, tetrahydrofuran dioxan and mixtures thereof.

14. The process of claim 13 wherein said water-miscible organic solvent is selected from the group consisting of acetone, ethanol, isopropyl alcohol, n-propanol, n-butanol and mixtures thereof.

15. The process of claim 11, 13 and 14 wherein said solvent is acetone or a homogeneous mixture of acetone and water.

16. The process of claim 11 wherein said improved form of Form I celiprolol hydrochloride is recovered by filtration or centrifuging.

17. The process of claim 11 wherein celiprolol base has a moisture content of less than 5% w/w.

18. The process of claim 16 wherein celiprolol base has a moisture content between 2-5% w/w.

19. The process of claim 11 wherein celiprolol base is obtained by drying at a temperature less than 70ºC.

20. The process of claim 19 wherein celiprolol base is obtained by drying at a temperature less than 55ºC.